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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/372,380	08/11/1999	ROMAN M. CHICZ	08191/008003	1336

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EXAMINER
ZHOU, SHUBO

ART UNIT	PAPER NUMBER
1631	12

DATE MAILED: 12/31/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/372,380	CHIEZ ET AL.	
	Examiner	Art Unit	
	Shubo "Joe" Zhou	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,17-21 and 43-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 17-21, 43-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment and request for reconsideration in Paper #11, filed on 10/1/01, is acknowledged and the amendments entered.

Applicant's arguments in response to the previous Office Action, mailed 3/23/01, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections from previous Office actions not reiterated herein are hereby withdrawn. The following rejections and/or objections are either reiterated from the previous Office actions, or newly applied, and constitute the complete set presently being applied to the instant application.

Applicant is hereby notified that the required timing for the correction of drawings has changed. See the last 6 lines on the sheet which is attached entitled "Attachment for PTO-948 (Rev. 03/01 or earlier)". It is noted that a PTO-948 was mailed with Paper No. 8 on 3/23/01. Due to the above notification, applicant is required to submit drawing corrections within the time period set for responding to this Office action. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office action.

Claim Rejections-35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been**

obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14, 17-21, and 43-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brusic et al. (Nucleic Acids Research, 1998, Vol. 26, No. 1, pages 368-371) in view of Jeff Seale (The GroEL-Protein Interaction Database, The Chaperonin Home Page: http://bioc09.uthscsa.edu/~seake/Chap/chap.html, May 26, 1998), and in further view of Flanagan et al. (US patent No. 5,795,734, date of patent: Aug. 18, 1998, application filing date: May 31, 1995) and Duan et al. (Proc. Natl. Acad Sci USA, 1995, 92(14):6459-6463).

This rejection is reiterated from the previous Office action and maintained for reasons of record.

Applicants' arguments focus on the ground that the combination of the references does not teach or suggest (1) the ligand profile is representative of any particular cell or cell type (page 7, second paragraph) and (2) the VHL protein is not a multi-ligand binding receptor with at least 10 different proteins binding thereto, with details encompassing pages 5-10. This is not found persuasive because of the following:

As stated in the Office action, among other things, the disclosed profile of MHC class I receptor is characteristic of T-cell. This is suggested throughout the text of Brusic et al. as evidenced by reciting T-cells on page 368, paragraphs 1 and 2, page 369, left column, paragraph 1, page 370, left column, etc. etc. It is well-known that MHC class I is a characteristics of T-cells and the receptor binding profile is certainly characteristic of T-cell. It is also well-known that the receptor binding profile for a given cell type, such as T-cell, changes as environmental condition of the cell changes such as temperature, pH value, and the presence of regulatory molecules. Thus, the binding profile by Brusic et

al. is at least characteristic of T-cell type. Therefore, the combination of the references does teach/suggest the profile is characteristic of a cell type.

Although it is not known whether the VHL protein binds to at least 10 proteins to qualify as a multi-ligand receptor as defined by applicants, it is certain from Brusic et al. that the MHC class I receptor binds to at least 10 proteins/peptides and qualifies as a multi-ligand receptor. Thus, the combination of the references does teach/suggest a multi-ligand receptor.

Newly added claims 84-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brusic et al. (Nucleic Acids Research, 1998, Vol. 26, No. 1, pages 368-371) in view of Jeff Seale (The GroEL-Protein Interaction Database, The Chaperonin Home Page: http://bioc09.uthscsa.edu/~seake/Chap/chap.html, May 26, 1998), and in further view of Flanagan et al. (US patent No. 5,795,734, date of patent: Aug. 18, 1998, application filing date: May 31, 1995) and Duan et al. (Proc. Natl. Acad Sci USA, 1995, 92(14):6459-6463).

Brusic et al. disclose a database of MHC-binding peptides, wherein MHC is class I or class II. Such a database is interpreted as being equivalent to a serial of profiles, as required in the instant claims. The disclosed profile of MHC class I receptor is characteristic of T-cell type (see page 369, left column). Each individual ligand is characterized based on at least three of the chemical or biological attributes including peptide sequence, MHC specificity, activity, binding affinity, source protein and anchor position, and at least 4617 peptides are represented for MHC class I receptor in the profile (see page 368, Abstract and page 371, Table 2), as required in the instant claims. These at least 6 attributes make obvious of the "at least three" or "at least two" or "at least one" attributes, as required in the instant claims. Brusic et al. also disclose

that a second ligand profile, i.e. the ligand profile for MHC class II receptor, is combined with the first ligand profile, i.e. the ligand profile for the MHC class I receptor above, to form part of the database, which second ligand profile includes at least 5394 peptides (see page 371, Table 2), as required in the instant claims. Brusic et al. further disclose that the database includes a set of ligand profiles comprising a first ligand profile comprising ligands of human MHC class I in a human T-cell and a second ligand profile comprising ligands of mouse MHC class I in a mouse T-cell. It is obvious to an ordinary artisan in the field that such difference in profile is due to the difference in genetic background, as required in the instant claim. Brusic et al. do not disclose a set of profile of a cell from a diseased individual. However, Brusic et al. motivate "combining data generated by diverse sources" (see page 371) and utilizing the database in research of cancer and autoimmunity (see page 370). Thus, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use the teachings and/or motivations of Brusic et al. to include in the database ligand profiles from cells with different status, healthy or diseased, human or non-human, or profiles from different sources, cells or tissues, as required in the instant claims.

Brusic et al. do not disclose ligand profiles comprising ion fragmentation patterns, but strongly suggest and motivate linking the ligand database with other databases such as SWISS-PROT, PIR and make the database accessible via Internet (see page 370 left column). Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use the teachings and/or motivations of Brusic et al. to link the ligand profile database to other databases so that one can retrieve other information from the other databases about a particular peptide in the ligand database, such as the ion fragmentation pattern of a particular protein from many databases available.

Brusic et al. do not disclose ligand profiles for receptors that are not an MHC class I or MHC class II receptors, but motivate combining data from different sources and linking the database with other databases. Jeff Seale disclose a ligand profile for a chaperonin protein GroEL comprising 31 ligand proteins, which GroEL is not an an MHC class I or MHC class II receptors, but a chaperonin, as required in the instant claims. The profile comprises at least three chemical or physical attributes including ligand name, release requirements and reference number (see pages 1-4).

Brusic et al. do not disclose a laboratory research method for generating a ligand profile but motivate such in that they collected the MHC ligands discovered in the laboratories and reported in the literature in their database. Flanagan et al. disclose method of discovery of receptor ligands and generation of profile comprising contacting samples from a first cell containing ligands with receptor EPH to let bind, isolating the receptor-ligand complex, separating the ligands with the receptor, fractionating the ligands and generating a profile (see columns 38-39, 4 and 63). Flanagan et al. do not disclose providing a second sample of an given cell, but it is conceivable to an ordinary artisan in the art that simply repeating the steps disclosed by Flanagan et al. for another sample of a cell which is essentially identical to the first cell would generate a second profile, as required in the instant claims.

Duan et al. disclose method for identifying protein ligands that bind to a protein VHL comprising providing first sample of a first cell (cos-7 cells) containing the ligands bound to VHL, providing antibody that binds to the receptor, isolating the VHL-ligand complex, separating VHL from its ligands, fractionating the ligands and generating a first profile of ligands (see pages 6459, 6461 and 6462). A second sample from a second cell (cos-7 cell transfected with mutant VHL) containing the VHL-ligand complex is used and a profile of ligand is generated (see page 6461, Figure 2). The first cell and the

second cell are essentially identical except that the second cell contains a mutant VHL (see Figure 2 legend). Although Duan et al. do not explicitly disclose, but it is obvious to an ordinary artisan in the art that the chemical or physical attributes for the separation of the ligands and thus the profiles include size, molecular weight, charge, pH value and sequence, wherein the sequences and charge of two of the ligands were determined after fractionation, as required in the instant claims. Duan et al. do not explicitly disclose use of a column for the isolating and separating as required in the instant claim, but it is obvious to an ordinary artisan in the art that the sucrose gradient for centrifugation is in a column (see page 6459, right column and page 6462, Figure 5). Duan et al. also disclose a process comprising providing a sample of lysate of cos-7 cells transfected with a mutant receptor, which sample comprises a first plurality of ligands bound to a first receptor, i.e. the wild-type VHL present in the original cos-7 cells and a plurality of ligands bound to a second receptor, i.e. the mutant VHL resulted from the transfected VHL, isolating the first and second VHL form the sample, separating the ligands from the receptors, fractionating the ligands and generating a first profile and a second profile, each of which profiles distinguishes among the ligands on the basis of molecular weights (see page 6459 "Materials and Methods" and page 6463, Figure 6). Duan et al. further disclose a process of comparing a first sample to a reference sample comprising producing the ligand profile of a mutant VHL, Y98H using the methods discussed above, providing a reference profile of the wild type VHL, comparing the two profiles for differences and similarities (see page 6463, Figure 6). The cells containing the wild type VHL is interpreted as healthy cells and the ones containing the mutant VHL is interpreted as diseased cells, as required in the instant claims. Also, the first cell sample comprises cells cultured in the presence of a test compound, i.e. the mutant VHL, but the reference cell sample does not (see page 6459, "Materials and Methods"), as

required in the instant claims. Duan et al. also disclose that the reference cell sample comprises cells cultured in the presence of a test compound, i.e. ARF6-FLAG, while the first cell sample does not (see lane 2 for the reference sample and lane 3 for the first sample in Figure 6, page 6461), as required in the instant claims.

It is noted that due to the broad meaning of the terms "receptor", "ligand" and "profile", the protein VHL is interpreted as a receptor, and the proteins it binds to are interpreted as ligands. The gels containing different ligands after fractionation are interpreted as profiles.

Thus, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use the teachings and/or suggestions/motivations of Brusic et al., Jeff Seale, Flanagan et al. and Duan et al. to develop the methods and generate the ligand profiles as disclosed in the instant application. There would have been a reasonable expectation of success because the combination of the references teach and/or suggest all the claim limitations and provide details of procedures.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to:
Shubo "Joe" Zhou, Ph.D., whose telephone number is (703) 605-1158. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst Tina Plunkett whose telephone number is 703)-305-3524, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

S. "Joe" Zhou, Ph.D.

Patent Examiner

MICHAEL BORIN, PH.D
PRIMARY EXAMINER